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10/662,430	09/16/2003	Steven M. Ruben	9593-034	2285

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,430	RUBEN, STEVEN M.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-15 are pending and are being acted upon in this Office Action.

2. The disclosure is objected to for failing to comply with the requirement of 37 C.F.R. 1.821(d), SEQ ID NO is required for page 47, paragraphs 0211 and 0212, Appropriate correction is required.

3. The disclosure is objected to because of the following informality: "die" on page 15, line 5 should have been "the". Appropriate action is required.

4. Applicant is reminded that declaration, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application 08/816,981 do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-6 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the plasmid containing the human cDNA with ATCC Deposit No. 97448 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the plasmid containing the human cDNA with ATCC Deposit No. 97448 have been deposited under the Budapest Treaty and that the plasmid containing the human cDNA with

ATCC Deposit No. 97448 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or **for the enforceable life of the patent whichever is longer**. See 37 CFR 1.806.

If the deposit has not been made under the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

7. Claims 7-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a purified protein comprising a polypeptide sequence selected from the group consisting of (a) amino acids 1 to 281 of SEQ IDNO: 2, (b) an amino acid sequence encoded by the human cDNA contained in ATCC Deposit Nol 97448, (2) a composition comprising a purified protein comprising a polypeptide sequence selected from the group consisting of (a) amino acids 1 to 281 of SEQ IDNO: 2, (b) an amino acid sequence encoded by the human cDNA contained in ATCC Deposit No 97448 and a pharmaceutically acceptable carrier for detection assays (3) a purified protein comprising said amino acid sequences and a heterologous sequence; **does not** reasonably provide enablement for (1) *any* purified protein comprising a polypeptide sequence selected from the group consisting of (a) amino acids 1 to 281 of SEQ ID NO: 2, except for 1 to 5 conservative amino acid substitutions; (b) amino acids 1 to 281 of SEQ ID NO: 2, except for 5 to 10 conservative amino acid substitutions; (c) amino acids 39 to 281 of SEQ ID NO: 2, except for 1 to 5 conservative amino acid substitutions; and (4) amino acids 39 to 281 of SEQ ID NO: 2, except for 5 to 10 conservative amino acid substitutions (2) a composition comprising any purified protein mentioned above and a pharmaceutically carrier, (3) *any* purified protein which binds to any antibody specific to a polypeptide having an amino acid sequence of SEQ ID NO: 2, and (4) *any* purified protein comprising encoded by a polynucleotide which hybridizes to the human cDNA contained in ATCC Deposit No 97448, at 65°C in a hybridization buffer consisting of 7% SDS, 0.5M NaPO4 (pH 7.1), followed by washing in 0.5 x SSC and 0.1% SDS at 60°C; wherein said polypeptide has a biological activity such as binding an antibody specific to the polypeptide of SEQ ID NO: 2; inducing apoptosis of a

cell line derived from pathological tissue; and inducing apoptosis in T cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a purified protein from human comprising amino acids 1 to 281 of SEQ ID NO: 2 encoded by the deposited human cDNA contained in ATCC Deposit No 97448 for radioimmune assay or binding assays. The specification discloses compositions comprising AIM-I polypeptide intended for treatment of autoimmune disease, graft versus host disease, lymphadenopathy and among other things (pages 3-6).

The specification does not teach how to make any purified protein mentioned above because there is insufficient guidance as to which 1-5, or 5 to 10 amino acids within 1-281 of SEQ ID NO: 2 or which 1-5, or 5 to 10 amino acids within 39 to 281 amino acids of SEQ ID NO: 2 to be substituted for which amino acids that the resulting polypeptide maintained its structure and function such as inducing apoptosis in T cell or cell line derived from pathological tissue, much less for maintaining binding to any or all antibody that binds to the polypeptide of SEQ ID NO: 2. There is a lack of working examples demonstrating that any undisclosed polypeptide ever induces apoptosis or binds to any antibody specific to SEQ ID NO: 2. Even if the polypeptide binds to antibody that binds to polypeptide of SEQ ID NO: 2, binding does not equal to inducing apoptosis.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Further, there is a lack of working example demonstrating any undisclosed protein binds to any antibody that binds to SEQ ID NO: 2.

It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Trabzuni *et al* teach that a single amino acid substitution from Cys230 to serine residue (conservative substitution) or cysteine to glycine (see page 506, site-directed mutation of TRAIL, in particular) fails to induce apoptosis in normal colon cells (Figures 2 and 3, page 508, col. 2, in particular).

Krieg *et al* teach that TRAIL splice variants such as TRAIL-β and TRAIL-γ loss apoptotic potential (See entire document, page 923, Figure 4, abstract, in particular).

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular). Given the indefinite number of polypeptide sequence, there is insufficient working example demonstrating all undisclosed protein comprising any polypeptide sequence mentioned above is effective for inducing apoptosis, much less for the intended use such as treating all autoimmune disease. Further, there is a lack of working example demonstrating all undisclosed protein bind to any antibody that binds to SEQ ID NO: 2. Given the lack of guidance and in vivo working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NOS: 2 that after substitution, deletion, insertion and/or modification will retain both structure and have similar function is unpredictable.

With regard to claim 15, there is insufficient guidance as to the structure of the polynucleotide that hybridizes to the human cDNA contained in ATCC Deposit No 97448 without the polynucleotide sequence, let alone the undisclosed polynucleotide encodes a protein that induces apoptosis in any cell line derived from all pathological tissue or T cells. Any polynucleotide fragment could hybridize to the nucleotide encoding amino acids 1 to 281 of SEQ

ID NO: 2, or 39 to 281 of SEQ ID NO: 2 or nucleotide encoding the amino acid sequence encoded by the human cDNA contained in ATCC Deposit NO. 97448. However, Binding does not necessary equal to having the same function such as inducing apoptosis. The state of the prior art as exemplified by Wallace *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728; there is no working example that the polynucleotide binding to the polynucleotide encoding the full-length polypeptide or the soluble polypeptide has biological activity such as inducing T cell apoptosis. Further, antibody specific to polypeptide of SEQ ID NO: 2 does not mean that the claimed polypeptide has the specific apoptotic function because the antibody may bind to a peptide that just happened to share some amino acid residues identical to SEQ ID NO: 2.

Given the lack of guidance as to structure of the polypeptide encoded by the polynucleotide which hybridizes to the human cDNA contained in ATCC Deposit No. 97448, and the lack of sufficient working examples demonstrating that all purified protein binds to any antibody specific to the polypeptide of SEQ ID NO: 2, it is unpredictable which undisclosed protein produced by a process mentioned above is effective for any purpose.

With regard to composition comprising any polypeptide mentioned above, in addition to the lack of guidance as how to make any polypeptide mentioned above, there is inadequate teaching and in vivo working example how to use the undisclosed polypeptide for treating all disease such as autoimmune disease, graft versus host disease, and tumor. Even if the composition comprising the purified protein comprising the full-length polypeptide or the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No 97448, the specification discloses that the intended use for the claimed composition is for treatment of all disease such as all autoimmune disease, graft versus host disease, lymphadenopathy and among other things (pages 3-6). For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of

the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 7-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* or *all* purified protein comprising a polypeptide sequence selected from the group consisting of amino acids "39 to 281" of SEQ ID NO: 2, except for 1 to 5, or 5 to 10 conservative amino acid substitutions, (2) a composition comprising *any* or *all* purified protein comprising a polypeptide sequence selected from the group consisting of amino acids "39 to 281" of SEQ ID NO: 2, except for 1 to 5, or 5 to 10 conservative amino acid substitutions; (3) a purified protein which binds to any antibody specific to a polypeptide having an amino acid sequence of SEQ ID NO: 2 and (4) *any* purified protein comprising encoded by a polynucleotide which hybridizes to the human cDNA contained in ATCC Deposit No 97448, at 65°C in a hybridization buffer consisting of 7% SDS, 0.5M NaPO4 (pH 7.1), followed by washing in 0.5 x SSC and 0.1% SDS at 60°C; wherein said polypeptide has a biological activity such as binding an antibody specific to the polypeptide of SEQ ID NO: 2.

The specification discloses only a purified protein from human comprising amino acids 1 to 281 of SEQ ID NO: 2 encoded by the deposited human cDNA contained in ATCC Deposit No 97448 for radioimmune assay or binding assays. The specification discloses compositions comprising AIM-I polypeptide intended for treatment of autoimmune disease, graft versus host disease, lymphadenopathy and among other things (pages 3-6).

Other than the specific purified protein mentioned above, there is inadequate written description about the structure associated with function of any purified protein as set forth in claims 7-8 because there is inadequate written description about which 1 to 5 or 5 to 10 amino acids within 1-281 of SEQ ID NO: 2 or which 1 to 5 or 5 to 10 amino acids within amino acids 39 to 281 to be substitute for which undisclosed amino acids. Further, there is inadequate written description about the protein that binds to all antibody specific to a polypeptide having an amino acid sequence of SEQ ID NO: 2 without the amino acid sequence because the undisclosed antibody could bind to a fragment of a protein happened to have a stretch of amino acids identical to SEQ ID NO: 2. There is inadequate written description about the epitope to which the

undisclosed antibody binds. With regard to claim 15, there is inadequate written description about the structure of the protein encoded by the polynucleotide which hybridizes to the human cDNA contained in ATCC Deposit No 97448 without the polynucleotide sequence, much less about the protein binds to any antibody specific to the polypeptide of SEQ ID NO: 2. An antibody specific to polypeptide of SEQ ID NO: 2 does not mean that the claimed polypeptide has the specific apoptotic function because the antibody may bind to a peptide or an epitope that just happened to share some amino acid residues identical to SEQ ID NO: 2. Binding does not necessary equal to inducing apoptosis.

Finally, the specification discloses only one polypeptide comprising 1-281 of SEQ ID NO: 2 which encoded by the human cDNA contained in ATCC Deposit No 97448 that induces apoptosis in T cells, the other proteins and the corresponding polynucleotides are not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

"A purified protein…39 to 281 of SEQ ID NO: 2" in Claim 1 represents a departure from the specification and the claims as originally filed.

"…amino acids 39 to 281 of SEQ ID NO: 2, except for 1 to 5 conservative amino acid substitutions; and amino acids 39 to 281 of SEQ ID NO: 2, except for 5 to conservative amino acid substitutions" in claim 7 represents a departure from the specification and the claims as originally filed.

"A …binding an antibody specific to polypeptide of SEQ ID NO: 2; (b) inducing apoptosis of a cell line derived from pathologic tissue; and (c) inducing apoptosis in T cells" in

claim 15 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrases come from.

10. The filing date of the instant claims 1, 3, 5, 6, 7, 10-15 are deemed to be the filing date of the instant application 9/16/03, as the provisional 60/013,405 is drawn only to a purified protein comprising a polypeptide sequence selected from the group consisting of (a) the amino acid sequence of the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit No 97448 and (b) the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No 97448 and a composition comprising said purified protein and a pharmaceutically acceptable carrier, and thus does not support the claimed limitation such as "A purified protein...**39 to 281** of SEQ ID NO: 2" in Claims 1 and 3, "...amino acids **39 to 281** of SEQ ID NO: 2, except for 1 to 5 conservative amino acid substitutions; and amino acids **39 to 281** of SEQ ID NO: 2, except for 5 to conservative amino acid substitutions" in claims 7, 10-12, and "binding an antibody specific to the polypeptide of SEQ ID NO: 2" as set forth in claims 14-15 of the instant application.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 1, 3, 5-6, 14, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 6,030,945 (issued Feb 29, 2000; PTO 892).

The '945 patent teaches a purified human Apo-2 ligand protein comprising a polypeptide sequence of SEQ ID NO: 1 that is 100% identical to the claimed amino acids 1 to 281 of SEQ IDNO: 2 (See Figure 1A of '945 patent, in particular) wherein the reference protein induces apoptosis in human lymphoid cell such as cell line derived from tissue such as EBV transformed human B cells (See column 33, lines 61 bridging column 34, in particular). The '945 patent teaches various purified active protein fragments comprising amino acid sequences from 41-281 or 15-281 of the claimed SEQ ID NO: 2 (See column 3, lines 1-8, in particular). The term "comprising" is open-ended. It expands the claimed amino acids 39 to 281 of SEQ ID NO: 2 to include the reference protein fragments comprising amino acid sequences from 41-281 or 15-281 of the claimed SEQ ID NO: 2. The '945 patent further teaches various chimeric protein comprising the reference SEQ ID NO: 1 fused to a heterologous polypeptide sequence such as bacterial or viral antigen or His to facilitate purification (See column 17, lines 43-45, Example 3, column 33, column 19, lines 36-43, in particular). The '945 patent teaches a composition comprising the reference polypeptide and a pharmaceutically acceptable carrier such as saline solution for treating tumor (See column 20, lines 41-455, in particular). The '945 patent further teaches that the reference polypeptide Apo-2 ligand binds to polyclonal or monoclonal antibody that is specific for the reference polypeptide Apo-2 ligand, which is 100 % identical to the claimed polypeptide of SEQ ID NO: 2 (See column 23-24, in particular). Again, the term "comprising" is open-ended. It expands the claimed fragment to include additional amino acid at either or both ends to include the reference polypeptide. The reference protein is produced by a process of expressing in host cell such as human 293 cells a nucleic acid encoding amino acids 1 to 281 of the reference SEQ ID NO: 1 (See column 30, Example 2, bridging column 31, in particular). The reference purified protein comprises a heterologous polypeptide sequence such as Myc or poly His sequence or epitope tag sequence (See column 31, line 15-26, in particular). Claim 15 is included in this rejection because the reference protein is 100% identical to the claimed protein and the reference polynucleotide therefore would hybridize to the claimed human cDNA contained in ATCC Deposit No 97448 and induces apoptosis. Thus, the reference teachings anticipate the claimed invention.

14. Claims 1, 3, 5-7, and 10-15 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,763,223 (issued June 1998, PTO 892).

The '223 patent teaches a purified protein such as TRAIL comprising a polypeptide sequence that is that is 100% identical to the claimed amino acids 1 to 281 of SEQ IDNO: 2 (See SEQ ID NO: 2 of '945 patent, in particular) wherein the reference protein induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See column 30, lines 18-51, Table 1, in particular). The '223 patent further teaches a purified soluble protein comprising the extra cellular domain (amino acids 39-281) of the reference SEQ ID NO: 2 (See col. 2, line 45-49, column 4, line 66 bridging col. 5, line 1, in particular). The '223 patent also teaches fusion protein comprising heterologous polypeptide such as FLAG or Fc fused to the reference protein and fragment thereof (See column 9 lines 65 bridging col. 10, Example 11 at col. 31, Example 7 at col. 28, in particular). The reference proteins such as full-length TRAIL (amino acids 1-281 of the reference SEQ ID NO: 2) and soluble TRAIL (amino acids 39 to 281 of SEQ ID NO: 2) also bind to antibody that is specific to the claimed polypeptide of SEQ ID NO: 2 (See column 25, Example 4, line 29-36, in particular). The reference full length protein TRAIL comprises a polypeptide sequence that is 281 amino acids and has a biological activity such as induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See column 30, lines 18-51, Table 1, in particular). The '223 patent also teaches various protein fragment such as soluble TRAIL (39 to 281 of reference SEQ ID NO: 2) which is a fragment of the claimed amino acids 1 to 281 of SEQ ID NO: 2 and has biological activity such as inducing apoptosis (See col. 2, line 45-49, column 4, line 66 bridging col. 5, line 1, in particular) or binding to antibody that is specific to the claimed polypeptide of SEQ ID NO: 2 (See column 25, Example 4, line 29-36, in particular). The '223 patent also teaches a composition comprising the reference protein and a pharmaceutical acceptable carrier such as saline (See col. 18, lines 58 bridging col. 19, lines 1-5, in particular). The '223 patent further teaches various protein TRAIL variant comprising the reference full-length polypeptide (1 to 281 of reference SEQ ID NO: 2) or soluble fragment (39 to 281 of reference SEQ ID NO: 2) in which one or more amino acid residues are conservatively substituted and wherein the modified polypeptide retains its biological activity of a native TRAIL (See col. 7, lines 40-62, in particular). The '223 patent also teaches conservative substitution such as one aliphatic residue for another such as Ile, Val, Leu or Ala (See col. 7, lines 57-59, in particular). The '223 patent teaches the reference protein is produced by a process comprising

expressing in a host cell such as prokaryotic host cell, yeast host cell, or CHO cell the reference nucleic acid encoding the reference full-length TRAIL protein (1 to 281 or SEQ ID NO: 2) or the reference soluble TRAIL protein (39-281 of SEQ ID NO: 2) (See col. 11 to col. 15, in particular). The '223 patent also teaches TRAIL protein variants comprising an amino acid sequence that is at least 90% identical to the reference amino acid sequence of SEQ ID NO: 2 that retains the native TRAIL biological activity (See col. 52-66, in particular). Claim 15 is included in this rejection because the reference protein is 100% identical to the claimed protein and the reference polynucleotide therefore would hybridize to the claimed human cDNA contained in ATCC Deposit No 97448 and induces apoptosis. Thus, the reference teachings anticipate the claimed invention.

15. Claims 1-6, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Wiley *et al* (Immunity 3: 673-682, Dec 1995; PTO 892).

Wiley *et al* teach a purified protein such as TRAIL comprising a polypeptide sequence of 2 that is that is 100% identical to the claimed amino acids 1 to 281 of SEQ IDNO: 2 (Fig. 1, in particular) wherein the reference protein induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See Table 1 on page 678, Fig 3, lane 4, in particular). Wiley *et al* teach a purified soluble protein which is a fragment of TRAIL comprising the extra cellular domain (amino acids 95-281) of the reference polypeptide (See Fig 7 on page 679, page 675, column 1, in particular) wherein the reference protein induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See Table 1 on page 678, Fig 3, lane 4, in particular). The reference protein further comprises a heterologous polypeptide such as FLAG (See page 680, column 1, Purification of Soluble TRAIL, in particular). Wiley *et al* teach a composition comprising the reference TRAIL and pharmaceutically acceptable carrier such as TRIS (See page 676, caption of Fig 4, in particular). Claim 4 is included in this rejection because the reference polypeptide is 100% identical to the claimed polypeptide encoded by the human cDNA contained in the deposited cDNA. Since the claimed protein is identical to the reference protein TRAIL, the antibody specific to the claimed SEQ ID NO: 2 would also bind to the reference protein. Claim 15 is included in this rejection because the reference protein is 100% identical to the claimed protein and the reference polynucleotide therefore would hybridize to the claimed human cDNA contained in ATCC Deposit No 97448 and induces apoptosis in various cell lines derived from

pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See Table 1 on page 678, Fig 3, lane 4, in particular). Thus, the reference teachings anticipate the claimed invention.

16. Claims 1-15 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,030,945 (filed Jan 9, 1996).

The '945 patent teaches a purified human Apo-2 ligand protein comprising a polypeptide sequence of SEQ ID NO: 1 that is 100% identical to the claimed amino acids 1 to 281 of SEQ IDNO: 2 (See Figure 1A of '945 patent, in particular) wherein the reference protein induces apoptosis in human lymphoid cell such as cell line derived from tissue such as EBV transformed human B cells (See column 33, lines 61 bridging column 34, in particular). The '945 patent teaches various purified active protein fragments comprising amino acid sequences from 41-281 or 15-281 of the claimed SEQ ID NO: 2 (See column 3, lines 1-8, in particular). The term "comprising" is open-ended. It expands the claimed amino acids 39 to 281 of SEQ ID NO: 2 to include the reference protein fragments comprising amino acid sequences from 41-281 or 15-281 of the claimed SEQ ID NO: 2. The '945 patent further teaches various chimeric protein comprising the reference SEQ ID NO: 1 fused to a heterologous polypeptide sequence such as bacterial or viral antigen or His to facilitate purification (See column 17, lines 43-45, Example 3, column 33, column 19, lines 36-43, in particular). The '945 patent teaches a composition comprising the reference polypeptide and a pharmaceutically acceptable carrier such as saline solution for treating tumor (See column 20, lines 41-455, in particular). The '945 patent further teaches that the reference polypeptide Apo-2 ligand binds to polyclonal or monoclonal antibody that is specific for the reference polypeptide Apo-2 ligand, which is 100 % identical to the claimed polypeptide of SEQ ID NO: 2 (See column 23-24, in particular). Again, the term "comprising" is open-ended. It expands the claimed fragment to include additional amino acid at either or both ends to include the reference polypeptide. The reference protein is produced by a process of expressing in host cell such as human 293 cells a nucleic acid encoding amino acids 1 to 281 of the reference SEQ ID NO: 1 (See column 30, Example 2, bridging column 31, in particular). The reference purified protein comprises a heterologous polypeptide sequence such as Myc or poly His sequence or epitope tag sequence (See column 31, line 15-26, in particular). Claim 15 is included in this rejection because the reference protein is 100% identical to the claimed protein and the reference polynucleotide therefore would hybridize to the claimed human

cDNA contained in ATCC Deposit No 97448 and induces apoptosis. Thus, the reference teachings anticipate the claimed invention.

17. Claims 1-15 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 5,763,223 (filed June 1995, PTO 892).

The '223 patent teaches a purified protein such as TRAIL comprising a polypeptide sequence that is that is 100% identical to the claimed amino acids 1 to 281 of SEQ IDNO: 2 (See SEQ ID NO: 2 of '945 patent, in particular) wherein the reference protein induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See column 30, lines 18-51, Table 1, in particular). The '223 patent further teaches a purified soluble protein comprising the extra cellular domain (amino acids 39-281) of the reference SEQ ID NO: 2 (See col. 2, line 45-49, column 4, line 66 bridging col. 5, line 1, in particular). The '223 patent also teaches fusion protein comprising heterologous polypeptide such as FLAG or Fc fused to the reference protein and fragment thereof (See column 9 lines 65 bridging col. 10, Example 11 at col. 31, Example 7 at col. 28, in particular). The reference proteins such as full-length TRAIL (amino acids 1-281 of the reference SEQ ID NO: 2) and soluble TRAIL (amino acids 39 to 281 of SEQ ID NO: 2) also bind to antibody that is specific to the claimed polypeptide of SEQ ID NO: 2 (See column 25, Example 4, line 29-36, in particular). The reference full length protein TRAIL comprises a polypeptide sequence that is 281 amino acids and has a biological activity such as induces apoptosis in various cell lines derived from pathological leukemia such as Bjab, Ramos, U937 or T cell such as Jurkat cell (See column 30, lines 18-51, Table 1, in particular). The '223 patent also teaches various protein fragment such as soluble TRAIL (39 to 281 of reference SEQ ID NO: 2) which is a fragment of the claimed amino acids 1 to 281 of SEQ ID NO: 2 and has biological activity such as inducing apoptosis (See col. 2, line 45-49, column 4, line 66 bridging col. 5, line 1, in particular) or binding to antibody that is specific to the claimed polypeptide of SEQ ID NO: 2 (See column 25, Example 4, line 29-36, in particular). The '223 patent also teaches a composition comprising the reference protein and a pharmaceutical acceptable carrier such as saline (See col. 18, lines 58 bridging col. 19, lines 1-5, in particular). The '223 patent further teaches various protein TRAIL variant comprising the reference full-length polypeptide (1 to 281 of reference SEQ ID NO: 2) or soluble fragment (39 to 281 of reference SEQ ID NO: 2) in which one or more amino acid residues are conservatively substituted and wherein the modified polypeptide retains its biological activity of a native TRAIL

(See col. 7, lines 40-62, in particular). The '223 patent also teaches conservative substitution such as one aliphatic residue for another such as Ile, Val, Leu or Ala (See col. 7, lines 57-59, in particular). The '223 patent teaches the reference protein is produced by a process comprising expressing in a host cell such as prokaryotic host cell, yeast host cell, or CHO cell the reference nucleic acid encoding the reference full-length TRAIL protein (1 to 281 or SEQ ID NO: 2) or the reference soluble TRAIL protein (39-281 of SEQ ID NO: 2) (See col. 11 to col. 15, in particular). The '223 patent also teaches TRAIL protein variants comprising an amino acid sequence that is at least 90% identical to the reference amino acid sequence of SEQ ID NO: 2 that retains the native TRAIL biological activity (See col. 52-66, in particular). Claim 15 is included in this rejection because the reference protein is 100% identical to the claimed protein and the reference polynucleotide therefore would hybridize to the claimed human cDNA contained in ATCC Deposit No 97448 and induces apoptosis. Thus, the reference teachings anticipate the claimed invention.

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 10/662,429. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Instant claim 1 recites a purified protein comprising a polypeptide selected from the group consisting of: (a) amino acids 1 to 281 of SEQ IID NO: 2; (b) amino acids 39 to 281 of SEQ ID NO: 2; and (c) an amino acid sequence encoded by the human cDNA contained in ATCC Deposit No. 97448 (species).

Instant claim 2 of instant application recites the purified protein wherein said polypeptide is amino acids 1 to 281 of SEQ ID NO: 2.

Instant claim 3 of instant application recites the purified protein wherein said polypeptide is amino acids 39 to 281 of SEQ ID NO: 2.

The pending claim 1 of 10/662,429 recites A purified protein comprising a polypeptide sequence that is at least 70% identical to an amino acid sequence selected from the group consisting of: (a) amino acids 1 to 281 of SEQ m NO:2; (b) amino acids 39 to 281 of SEQ ID NO:2, wherein said polypeptide sequence has a biological activity selected from the group consisting of: (i) binding an antibody specific to the polypeptide of SEQ ID NO:2; (ii) inducing apoptosis of a cell line derived from pathologic tissue; and (iii) inducing apoptosis of T cells.

The pending claim 4 of 10/662,429 recites the purified protein of claim 1 wherein the polypeptide is at least 90% identical to amino acids 1 to 281 of SEQ ID NO:2.

The pending claim 5 of 10/662,429 recites the purified protein of claim 1 wherein said polypeptide sequence is at least 90% identical to amino acids 39 to 281 of SEQ ID NO:2.

The pending claim 6 of 10/662,429 recites the purified protein of claim 1 wherein said polypeptide sequence is at least 95% identical to amino acids 1 to 281 of SEQ ID NO:2.

The pending claim 7 of 10/662,429 recites the purified protein of claim 1 wherein said polypeptide sequence is at least 95% identical to amino acids 39 to 281 of SEQ ID NO:2.

Because the full length protein (amino acids 1 to 281 of SEQ ID NO: 2) of instant application is 100% identical to the protein (amino acids to 281 of SEQ ID NO: 2) encoded by the human cDNA contained in ATCC Deposit No. 97448 of 10/662,429, the instant protein is *at least* 70%, 90%, or 95% identical to full length amino acids 1 to 281 of SEQ ID NO: 2. Likewise, the soluble protein (amino acids 39 to 281) of instant application is *at least* 70%, 90%, or 95% identical to the soluble protein (amino acids 39 to 281) of 10/662,429. Since the protein of instant application is the same protein as that of 10/662,429, the functional properties of the protein (claim 1 of 10/662,429) would be an inherent properties of the protein.

Claim 5 of instant application recites the purified protein comprises a heterologous polypeptide sequence, which is not distinguishable from the purified protein comprises a heterologous polypeptide sequence in claim 2 of 10/662,429.

Claim 6 of instant application recites a composition comprising the purified protein comprising a polypeptide selected from the group consisting of: (a) amino acids 1 to 281 of SEQ IID NO: 2; (b) amino acids 39 to 281 of SEQ ID NO: 2; and (c) an amino acid sequence encoded by the human cDNA contained in ATCC Deposit No. 97448. Said composition is not distinguishable from a composition comprising the purified protein comprising a polypeptide sequence that is at least 70% identical to an amino acid sequence selected from the group consisting of: (a) amino acids 1 to 281 of SEQ m NO:2; (b) amino acids 39 to 281 of SEQ ID NO:2, wherein said polypeptide sequence has a biological activity selected from the group consisting of: (i) binding an antibody specific to the polypeptide of SEQ ID NO:2; (ii) inducing apoptosis of a cell line derived from pathologic tissue; and (iii) inducing apoptosis of T cells in claim 3 of 10/662,429 and in claims 13-14 and 17 of 10/662,429. Likewise, the same reasoning applies to claim 13 of instant application and claim27 of 10/662,429.

Claim 7 of instant application recites A purified protein comprising a polypeptide sequence selected from the group consisting of: (a) amino acids 1 to 281 of SEQ ID NO:2, except for 1 to 5 conservative amino acid substitutions; (b) amino acids 1 to 281 of SEQ ID NO:2, except for 5 to 10 conservative amino acid substitutions; (c) amino acids 39 to 281 of SEQ ID NO:2, except for 1 to 5 conservative amino acid substitutions, and (d) amino acids 39 to 281 of SEQ ID NO:2, except for 5 to 10 conservative amino acid substitutions (species) which anticipates the genus of Claim 18 of 10/662,429 since claim 18 of 10/662,429 recites A purified protein comprising a polypeptide sequence selected from the group consisting of: (a) amino acids 1-281 of SEQ ID NO:2 in which 1 to 5 amino acid residues are substituted, deleted or added; (b) amino acids 1-281 of SEQ m NO:2 in which 5 to 10 amino acid residues are substituted, deleted or added; (c) amino acids 1-38 of SEQ m NO:2 in which 1 to 5 amino acid residues are substituted, deleted or added; (d) amino acids 1-38 of SEQ ID NO:2 in which 5 to 10 amino acid residues are substituted, deleted or added; (e) amino acids 39-281 of SEQ ID NO:2 in which 1 to 5 amino acid residues are substituted, deleted or added; and (f) amino acids 39-281 of SEQ ID N0:2 in which 5 to 10 amino acid residues are substituted, deleted or added; wherein said polypeptide sequence has a biological activity selected from the group consisting of: (i) binding

an antibody specific to the polypeptide of SEQ ID NO:2; (ii) inducing apoptosis of a cell line derived from pathologic tissue, and (iii) inducing apoptosis of T cells.

Claim 8 of instant application recites the purified protein of claim 7 wherein said polypeptide sequence is amino acids 1 to 281 of SEQ ID NO: 2, except for 1 to 5 conservative amino acid substitutions (species). Claim 19 of 10/662,429 recites the purified protein of claim 18 wherein said polypeptide sequence is amino acids 1 to 281 of SEQ ID NO: 2, in which 1 to 5 amino acid residues are substituted, deleted, or added (genus). The species anticipates a genus. Likewise, the same reasoning for claims 9-11 of instant application applies to claims 20-24 of 10/662,429.

Claim 14 of instant application recites a purified protein which binds to an antibody specific to a polypeptide having an amino acid sequence of SEQ ID NO: 2. Claim 29 of 10/662,429 recites a protein comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of the purified protein of claim 25, wherein said protein has a biological activity selected from the group consisting of: (a) binding an antibody specific to the polypeptide of SEQ ID NO:2; (b) inducing apoptosis of a cell line derived from pathologic tissue, and (c) inducing apoptosis of T cells. Since the protein of instant application is 100% identical to the protein of 10/662,429, the protein is at least 90% identical to the amino acid sequence of SEQ ID NO: 2 and both proteins would expected to bind to the antibody specific to a polypeptide having an amino acid sequence of SEQ ID NO: 2 given a large stretch (90%) of identical amino acid sequence.

Claim 15 of instant application recites A purified protein comprising a polypeptide encoded by a polynucleotide which hybridizes to the human CDNA contained in ATCC Deposit No. 97448, at 650 C in a hybridization buffer consisting of 7% SDS, 0.5 M NaPO4 (pH 7.4), followed by washing in 0.5 X SSC and 0.1% SDS at 600 C; wherein said polypeptide has a biological activity selected from the group consisting of: (a) binding an antibody specific to the polypeptide of SEQ ID NO:2; (b) inducing apoptosis of a cell line derived from pathologic tissue; and (c) inducing apoptosis of T cells (species).

Claim 25 of 10/662,429 recites An purified protein produced by a process comprising: expressing in a host cell a nucleic acid encoding said protein so as to produce said protein, wherein the nucleic acid is selected from the group consisting of:

(a) a polynucleotide encoding amino acids 1 to 281 of SEQ m NO:2;

(b) a polynucleotide encoding amino acids 39 to 281 of SEQ ID NO:2;

(c) a polynucleotide encoding amino acids 1 to 281 of SEQ ID NO:2, except for 1 to 5 conservative amino acid substitutions;

(d) a polynucleotide encoding amino acids 1 to 281 of SEQ ID NO:2, except for 5 to 10 conservative amino acid substitutions;

(e) a polynucleotide encoding amino acids 39 to 281 of SEQ ID NO:2, except for 1 to 5 conservative amino acid substitutions;

(9 a polynucleotide encoding amino acids 39 to 281 of SEQ ID N0:2, except for 5 to 10 conservative amino acid substitutions;

(g) a polynucleotide encoding the amino acid sequence encoded by the human CDNA contained in ATCC Deposit No. 97448; and

(h) a polynucleotide that is complementary to a polynucleotide which hybridizes at 60OC in a hybridization buffer consisting of 0.5 X SSC and 0.1% SDS to a polynucleotide selected from the group consisting of:

(i) a polynucleotide encoding amino acids 1 to 281 of SEQ ID NO:2;

(ii) a polynucleotide encoding amino acids 39 to 281 of SEQ m NO:2; and

(iii) a polynucleotide encoding the amino acid sequence encoded by the human CDNA contained in ATCC Deposit No. 97448, wherein said polynucleotide encodes a polypeptide that has a biological activity selected from the group consisting of:

(aa) binding an antibody specific to the polypeptide of SEQ ID NO:2;

(bb) inducing apoptosis of a cell line derived from pathologic tissue; and

(cc) inducing apoptosis of T cells (genus). Therefore, the issuance a patent to instant claims (species) would anticipate claims of 10/662,429 (genus).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

22. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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